

Evaluation of Antioxidant and Hepatoprotective Activity of Plant Extract against CCl₄ Induced Toxicity in SD Rats

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Abstract:

The present study aim that *Alternanthera brasiliana* (AB) possesses significant hepatoprotective, antioxidant, and anti-inflammatory properties against CCl₄-induced liver injury. Phytochemical analysis revealed that AB extracts, particularly the hydroalcoholic and chloroform fractions, are rich in phenolics, flavonoids, terpenoids, and alkaloids, many of which are known for their bioactivity. In-vitro assays confirmed strong free radical scavenging and reducing power, consistent with the phytochemical profile. These findings suggest that the hepatoprotective efficacy of *Alternanthera brasiliana* is mediated through a synergistic interplay of antioxidant, anti-inflammatory, and antifibrotic mechanisms. The results highlight AB as a promising candidate for development as a natural hepatoprotective agent or adjunctive therapy in managing liver disorders associated with oxidative stress and inflammation

Keywords: LC–MS/MS, *Alternanthera brasiliana*, hepatoprotective efficacy, phenolics, flavonoids, terpenoids

Introduction

Lipid Peroxidation, Oxidative Stress, Necrosis, Fibrosis

Lipid peroxidation triggered by CCl₄ results in disruption of membrane integrity, increased permeability, and leakage of hepatic enzymes such as ALT, AST, and ALP into circulation, serving as biomarkers of liver injury. The progression of oxidative stress damages mitochondria and endoplasmic reticulum, impairing cellular energy metabolism and protein synthesis. Persistent oxidative injury stimulates Kupffer cells and hepatic stellate cells, promoting inflammation, collagen deposition, necrosis, and eventually fibrosis.

Antioxidants and Hepatoprotective Agents

Antioxidants are compounds that mitigate oxidative stress by neutralizing free radicals and reactive oxygen/nitrogen species. In hepatotoxicity, antioxidants restore redox balance, protect cellular membranes, and enhance tissue repair. Hepatoprotective agents may exert their activity through radical scavenging, inhibition of lipid peroxidation, stabilization of cell membranes, and upregulation of endogenous defense mechanisms.

Synthetic Hepatoprotective Agents (e.g., Silymarin) Have

Limitations: Although several synthetic and semi-synthetic hepatoprotective agents, such as silymarin, ursodeoxycholic acid, and corticosteroids, are available, their clinical use is often limited by side effects, inconsistent efficacy, and high costs. Silymarin, derived from *Silybum marianum*, is considered the gold standard hepatoprotective drug, yet it exhibits poor oral bioavailability and variable therapeutic outcomes.

Need for Safe, Natural Plant-Based Alternatives

Given the limitations of synthetic agents, the search for safe, effective, and affordable natural alternatives has gained momentum. Plant-based antioxidants and hepatoprotective agents offer a dual advantage: protection against oxidative stress and additional pharmacological benefits such as anti-inflammatory and immunomodulatory activities. Thus, evaluating the hepatoprotective potential of plant extracts

against CCl₄-induced hepatotoxicity not only validates their traditional use but also paves the way for novel therapeutic interventions.

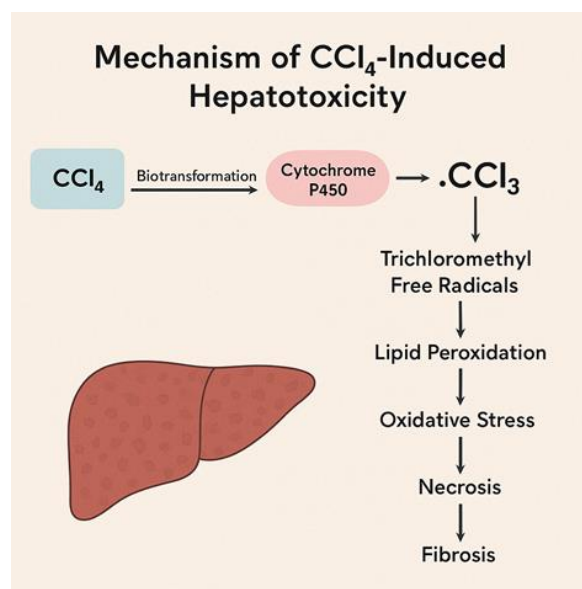


Figure 1: Mechanism of CCl₄-Induced Hepatotoxicity

Materials and Methods

Chemicals and Reagents

Carbon tetrachloride (CCl₄, 99% purity) was obtained from LOBA CHEMIE Pvt. Ltd. (Mumbai, India). Corn oil, DPPH, ABTS, Folin-Ciocalteu (FC) reagent, 2-thiobarbituric acid (TBA), trichloroacetic acid (TCA), reduced glutathione (GSH), DTNB, CDNB, DNPH, gallic acid, aluminium chloride, sulfanilamide, copper sulphate, thiourea, superoxide dismutase (SOD) assay kit, and BCA protein assay kit were purchased

from Sigma-Aldrich (St. Louis, MO, USA). Alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) diagnostic kits were purchased from Accurex Biomedical Pvt. Ltd. (MIDC Tarapur, Boisar, Maharashtra, India). Mouse-specific TNF- α and IL-1 β ELISA kits were procured from Thermo Fisher Scientific (USA). Primary antibodies (β -actin, MMP-2, MMP-9, TIMP-1, TGF- β , collagen I, α -SMA, Smad2/3, p-Smad2/3, IL-1 β , IL-18) and HRP-conjugated secondary antibodies were purchased from ABclonal and Jackson ImmunoResearch Laboratories Inc. (USA). All other chemicals used were of analytical grade.

Collection, Authentication, and Extraction of Plant Material
Leaves of *Alternanthera brasiliensis* (Family: Amaranthaceae) were collected from Guwahati, Assam, India on 9th August 2021. The plant was authenticated at the Assam Bioresource Centre (Accession No: ABRC-1047/21).

- The aerial parts were washed, shade-dried, and powdered.
- 100 g of powdered leaves were extracted with chloroform, methanol, and hydroalcohol (methanol:water = 60:40) solvents (1:10 w/v).
- The mixture was stirred every 24 h and filtered with Whatman No.1 filter paper.
- The filtrates were concentrated under reduced pressure using a rotary evaporator (40 °C, 90 rpm).
- Dried extracts were stored at 4 °C for further analysis.

Total Phenolic Content (TPC)

The phenolic content was determined using Folin-Ciocalteu reagent.

- 100 μ L of extract was mixed with 200 μ L FC reagent and 750 μ L of 7.5% Na₂CO₃.
- Incubated for 30 min, absorbance measured at 765 nm (SpectraMax i3x).
- Gallic acid was used as the standard.
- Results were expressed as mg gallic acid equivalent (GAE) per g extract.

Total Flavonoid Content (TFC)

Quercetin was used as standard.

- 100 μ L extract + 30 μ L 10% AlCl₃ + 30 μ L 5% NaNO₂.
- After 5 min, 200 μ L NaOH (1 M) was added.
- Absorbance was measured at 510 nm.
- Results were expressed as mg quercetin equivalent (QE) per g extract.

DPPH Radical Scavenging Assay

- 20 μ L extract was mixed with 200 μ L of 0.2 mM DPPH in methanol.
- Incubated 30 min in the dark, absorbance measured at 517 nm.
- Ascorbic acid was used as the standard.
- Radical scavenging activity (%) was calculated:

$$\% \text{ Inhibition} = 100\% \text{ Inhibition} = (1 - \text{OD}_{\text{control}} / \text{OD}_{\text{sample}}) \times 100$$

4.6 ABTS Radical Scavenging Assay

- ABTS stock prepared (7 mM ABTS + 2.4 mM potassium persulfate, incubated 16 h).
- Diluted to an absorbance of 0.7 at 734 nm.
- 20 μ L extract + 200 μ L ABTS solution, incubated 30 min.

- Absorbance at 734 nm recorded.
- Scavenging activity (%) calculated as in DPPH assay.

4.7 Phytochemical Analysis by LC-MS/MS

Extracts were derivatized and analyzed using Agilent Q-TOF LC/MS 6545 with Eclipse Plus C18 column (2.1 $\times$ 100 mm, 1.8 μ m).

- Mobile phase: (A) 0.1% formic acid in water, (B) 0.1% formic acid in acetonitrile.
- Gradient program: 0–20 min (5% B), 20–25 min (75% B), 25–26 min (5% B), 26–30 min (5% B).
- Flow rate: 0.2 mL/min, column at 40 °C.
- MS conditions: ion source temperature 320 °C, drying gas 11 L/min, nebulizer 35 psi, voltage $\pm$ 3500 V, scan m/z 50–3000.

Animals and Ethics Statement

- Male BALB/c mice (6 weeks, 20–25 g) were purchased from Jeeva Life Sciences (Hyderabad, India).
- Maintained in SPF conditions (24 $\pm$ 2 °C, 55 $\pm$ 15% humidity, 12 h light/dark cycle).
- Feed and water ad libitum.
- Experiments approved by IAEC, (Approval No: SAMK/PC/2024/31), CPCSEA guidelines followed.

Table.1: Experimental Design

Group	Treatment (n = number of mice)
Normal Control (n=6)	Corn oil (i.p.)
AB Control (n=6)	AB extract 400 mg/kg (p.o.) + corn oil
CCl ₄ Control (n=8)	20% CCl ₄ in corn oil (i.p.)
CCl ₄ + AB 200 (n=8)	AB extract 200 mg/kg (p.o.) + 20% CCl ₄ (i.p.)
CCl ₄ + AB 400 (n=8)	AB extract 400 mg/kg (p.o.) + 20% CCl ₄ (i.p.)

Biochemical & Oxidative Stress Assays

- Body weight, liver weight, liver index recorded.
- Serum biochemistry: ALT, AST, ALP, bilirubin, albumin, protein.
- Oxidative stress markers:
 - Nitrites (NO assay, 540 nm).
 - Lipid peroxidation (MDA, TBA assay, 532 nm).
 - GSH (DTNB assay, 412 nm).
 - GST (CDNB conjugation assay, 340 nm).
 - SOD (Sigma kit, 440 nm).
 - Vitamin C (DNPH method, 520 nm).

Histological Examination

- H&E staining: for cellular morphology.
- Masson's trichrome staining: for collagen deposition and fibrosis scoring.

qRT-PCR Analysis

- RNA extracted with TRIzol, cDNA synthesized with PrimeScript kit.
- qPCR performed with SYBR Green.
- Genes analyzed: TGF- β , fibronectin, IL-1 β , IL-18; RPL32 as internal control.
- Data analyzed by 2^{- $\Delta\Delta$ CT} method.

Statistical Analysis

Data presented as mean $\pm$ SEM.

- One-way ANOVA followed by Dunnett's multiple comparison test.
- GraphPad Prism 5.0 used.
- $p < 0.05$ considered statistically significant.

Result and Discussion

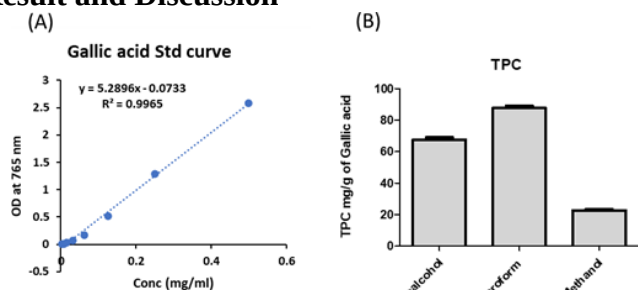


Figure.2: Standard curve (Gallic acid) for TPC; (B) TPC of extracts.

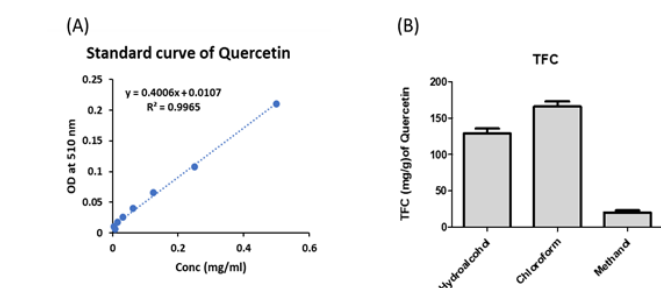


Figure.3: (A) Standard curve (Quercetin) for TFC; (B) TFC of extracts.

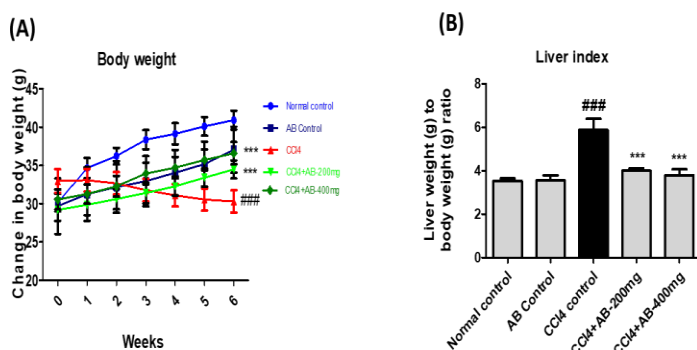


Figure.4: Body Weight, Liver Index, and Gross Morphology



Figure.5: (A) Body weight (wk1-6); (B) Liver index; (C) Liver morphology.

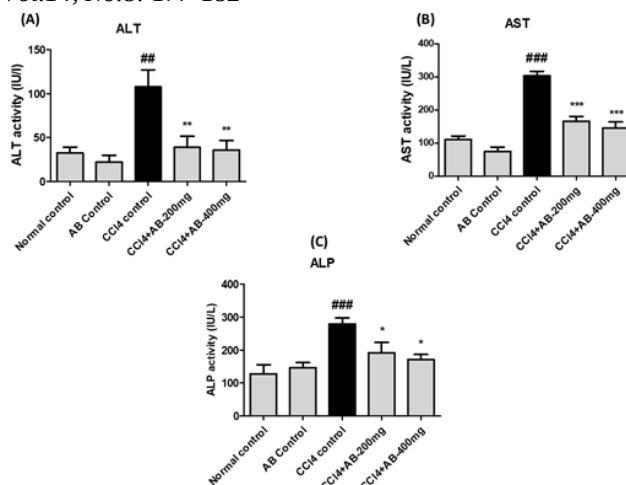


Figure6: (A) Effect of AB extract on ALT activity. (B) Effect of AB extract on AST activity. (C) Effect of AB extract on ALP activity. All experimental data were represented as mean $\pm$ SEM (n=6). Where ## $p < 0.01$, & ### $p < 0.001$ vs normal control group; * $p < 0.05$, ** $p < 0.01$, & *** $p < 0.001$ vs CCl4 control group.

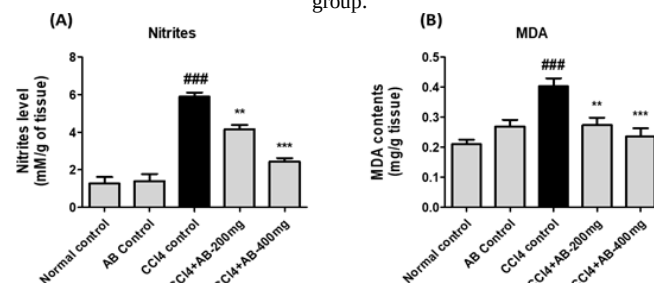


Figure7: (A) Effect of AB extract on nitrite level. (B) Effect of AB extract on MDA activity. All experimental results were presented as mean $\pm$ SEM (n=6). Where ## $p < 0.01$, & ### $p < 0.001$ vs normal control group; * $p < 0.05$, & ** $p < 0.01$, & *** $p < 0.001$ vs CCl4 control group.

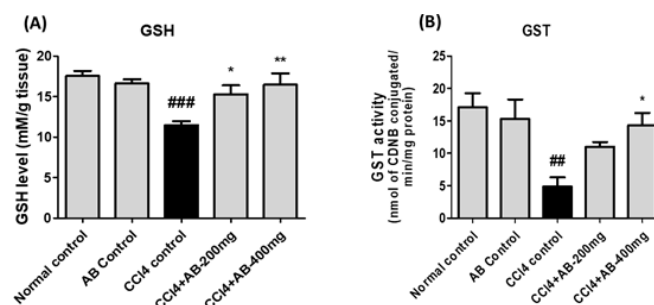
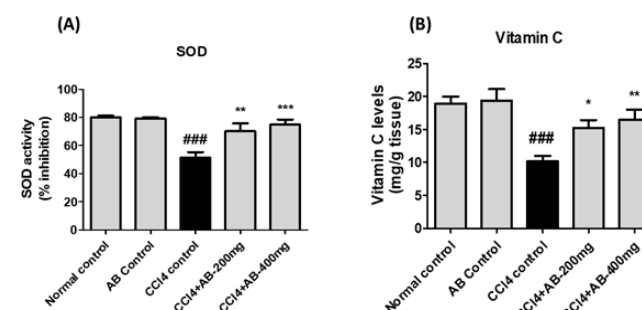


Figure.8: (A) Effect of AB extract on GSH level. (B) Effect of AB extract on GST activity. All data values were presented as mean $\pm$ SEM (n=6). Where ## $p < 0.01$, & ### $p < 0.001$ vs normal control group; * $p < 0.05$, & ** $p < 0.01$ vs CCl4 control group.



Figures 9: (A) Effect of AB extract on SOD activity. (B) Effect of AB extract on Vitamin C level. All obtained values were shown as mean $\pm$ SEM (n=6). Where ## $p < 0.001$ vs normal control group; * $p < 0.05$, ** $p < 0.01$, & *** $p < 0.001$ vs CCl4 control group.

Discussion

Phytochemical Composition and Antioxidant Capacity

The phytochemical screening revealed that *Alternanthera brasiliana* (AB) extracts, particularly the chloroform and hydroalcoholic fractions, are rich sources of phenolic and flavonoid compounds. The chloroform extract displayed the highest total phenolic content (TPC: 87.67 ± 1.44 mg GAE/g) and total flavonoid content (TFC: 165.69 ± 7.08 mg QE/g), while the hydroalcoholic extract also demonstrated considerable levels (TPC: 67.70 ± 1.39 mg GAE/g; TFC: 128.72 ± 6.92 mg QE/g). These results align with previous reports highlighting the importance of solvent polarity in extracting diverse classes of phytoconstituents, with chloroform efficiently solubilizing flavonoids, terpenoids, and other moderately polar compounds.

Antioxidant assays further supported the phytochemical findings. The hydroalcoholic extract exhibited the strongest free radical scavenging and reducing power in DPPH, ABTS, and FRAP assays, suggesting synergistic contributions from phenolics, flavonoids, and polar bioactive compounds. While the chloroform extract had higher TPC/TFC values, its comparatively lower antioxidant efficacy may indicate that not all phenolic constituents equally contribute to radical scavenging, and solvent-specific extraction plays a decisive role in the biological relevance of these phytochemicals. These findings underscore that AB harbors diverse antioxidant principles, potentially useful for counteracting oxidative stress-mediated hepatic injury.

In-vivo Hepatoprotective Effects

The CCl₄ model induced classical hepatotoxic manifestations, including reduced body weight, elevated liver index, morphological alterations, and elevated serum transaminases (ALT, AST, ALP). These biochemical and gross changes reflect hepatocellular necrosis, membrane leakage, and hepatic inflammation. Treatment with AB extracts (200 and 400 mg/kg) significantly improved body weight, normalized liver index, and restored serum enzyme activities toward baseline levels. The improvements were dose-dependent, with AB-400 showing superior efficacy, suggesting a strong protective role of the phytochemicals present in AB. Gross morphological observations further confirmed hepatoprotection, as AB-treated livers displayed smoother surfaces and near-normal architecture compared to the nodular and fibrotic appearance in CCl₄ controls. These outcomes demonstrate that AB mitigates hepatocellular damage, possibly through membrane stabilization and attenuation of oxidative injury.

Modulation of Oxidative and Nitrosative Stress

CCl₄ intoxication led to elevated lipid peroxidation (MDA) and nitrite accumulation, accompanied by depletion of endogenous antioxidants (GSH, GST, SOD, Vitamin C). These alterations are hallmarks of oxidative/nitrosative stress and impaired redox homeostasis. AB treatment significantly reduced nitrite and MDA levels while restoring antioxidant defenses in a dose-dependent manner. Restoration of enzymatic (GST, SOD) and

non-enzymatic (GSH, Vitamin C) antioxidants indicates that AB either enhances endogenous antioxidant machinery or directly neutralizes free radicals. Such effects correlate with the high phenolic and flavonoid contents observed, as these compounds are known to donate electrons, chelate pro-oxidant metals, and upregulate antioxidant enzyme expression. Thus, AB's hepatoprotective efficacy is closely linked to its capacity to modulate oxidative pathways.

Histopathology and Fibrosis Attenuation

Histological analysis provided strong morphological evidence of AB's hepatoprotective role. CCl₄-induced hepatic tissue displayed classic signs of necrosis, fatty degeneration, sinusoidal dilation, and fibrous bridging. These pathological changes were markedly attenuated in AB-treated groups. At 200 mg/kg, steatosis and fibrosis were reduced, while 400 mg/kg nearly restored normal hepatic architecture. Masson's trichrome staining further confirmed reduced collagen deposition, suggesting antifibrotic potential. This histological evidence complements the biochemical findings and underscores AB's role in preserving hepatocyte integrity, limiting fibrosis, and promoting hepatic regeneration.

Anti-inflammatory Effects

Inflammatory cytokines TNF- α and IL-1 β were significantly elevated in CCl₄-treated mice, consistent with their roles as mediators of hepatocellular inflammation, fibrosis, and apoptosis. AB extract reduced these cytokines in a dose-dependent manner, with AB-400 showing levels close to normal controls. This suggests that AB not only suppresses oxidative stress but also modulates inflammatory signaling pathways, possibly by downregulating NF- κ B-mediated transcription or inhibiting pro-inflammatory enzyme activity. The combined antioxidant and anti-inflammatory actions of AB therefore contribute synergistically to its hepatoprotective effect, reducing both the oxidative burden and inflammatory damage that drive chronic liver injury progression.

Overall Implications

Collectively, the findings indicate that *Alternanthera brasiliana* exerts robust hepatoprotective effects against CCl₄-induced hepatic injury through multiple mechanisms:

- **Antioxidant activity:** scavenging free radicals and restoring redox balance.
- **Anti-inflammatory effects:** suppression of pro-inflammatory cytokines (TNF- α , IL-1 β).
- **Membrane stabilization:** normalization of serum enzymes and gross morphology.
- **Antifibrotic potential:** reduction of collagen deposition and restoration of histoarchitecture.

The synergistic interplay of phytoconstituents detected by LC-MS/MS provides a mechanistic foundation for these effects. Given its favorable safety profile and broad bioactivity spectrum, AB represents a promising candidate for development as a natural hepatoprotective agent or dietary supplement.

Table.2: Antioxidant activities (per mg extract)

Assay	Hydroalcoholic	Chloroform	Methanol	Standard (Vit C)
DPPH (% scav.)	41.20 $\pm$ 0.69	16.25 $\pm$ 2.73	21.88 $\pm$ 2.87	IC ₅₀ = 0.228 mg/mL
ABTS (% scav.)	72.14 $\pm$ 1.19	12.56 $\pm$ 2.55	23.12 $\pm$ 2.10	IC ₅₀ = 0.233 mg/mL
FRAP (% red. power)	59.32 $\pm$ 2.42	37.52 $\pm$ 0.44	25.97 $\pm$ 0.84	IC ₅₀ = 0.164 mg/mL

Conclusion

The present study demonstrates that *Alternanthera brasiliana* (AB) possesses significant hepatoprotective, antioxidant, and anti-inflammatory properties against CCL₄-induced liver injury. Phytochemical analysis revealed that AB extracts, particularly the hydroalcoholic and chloroform fractions, are rich in phenolics, flavonoids, terpenoids, and alkaloids, many of which are known for their bioactivity. In-vitro assays confirmed strong free radical scavenging and reducing power, consistent with the phytochemical profile. LC–MS/MS chemical profiling further identified a diverse array of compounds, including cucurbitacins, curcumin, camptothecin, embelin, and momordicosides, providing a mechanistic basis for the observed bioactivities. In-vivo experiments demonstrated that AB significantly attenuated CCL₄-induced alterations in body weight, liver index, and gross morphology while restoring serum hepatic enzymes (ALT, AST, ALP) toward normal values. Oxidative and nitrosative stress markers (MDA, nitrite) were markedly reduced, and endogenous antioxidant defenses (GSH, GST, SOD, Vitamin C) were restored by AB treatment. Histopathological analysis confirmed the hepatoprotective effect, showing reduced steatosis, necrosis, and collagen deposition, with near-normal hepatic architecture at higher doses. Furthermore, AB down regulated inflammatory cytokines TNF- α , IL-1 β , indicating immunomodulatory potential. Overall, these findings suggest that the hepatoprotective efficacy of *Alternanthera brasiliana* is mediated through a synergistic interplay of antioxidant, anti-inflammatory, and antifibrotic mechanisms. The results highlight AB as a promising candidate for development as a natural hepatoprotective agent or adjunctive therapy in managing liver disorders associated with oxidative stress and inflammation

Conflict of Interests

The authors declare no conflict of interest

Ethics Approval: Not applicable

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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